PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61L 17/00, 31/00, C08L 69/00	A1	(11) International Publication Number: **WO 00/01426**
		(43) International Publication Date: 13 January 2000 (13.01.00)

(21) International Application Number: PCT/GB99/02154

(22) International Filing Date: 5 July 1999 (05.07.99)

(30) Priority Data:
9814609.5 7 July 1998 (07.07.98) GB

(71) Applicant *(for all designated States except US)*: SMITH & NEPHEW PLC [GB/GB]; 2 Temple Place, Victoria Embankment, London WC2R 3BP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: BROWN, Malcolm, W., R. [GB/GB]; 89 Wrenbeck Drive, Leeds LS21 2BP (GB).

(74) Agent: SMITH & NEPHEW GROUP RESEARCH CENTRE; Group Patents & Trade Marks Department, York Science Park, Heslington, York YO10 5DF (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BLEND OF BIORESORBABLE POLYMERS

(57) Abstract

Bioresorbable blends are presented for use in the manufacture of surgical implants. The blends comprise a bioresorbable copolymer and a further bioresorbable polymer.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

BLEND OF BIORESORBABLE POLYMERS

The present invention relates to bioresorbable polymeric compositions for use in the manufacture of medical devices, methods of making said compositions, medical devices made from said compositions and methods of treatment of the human or animal body involving such devices.

There is a need for surgical repair devices such as sutures, bone plates, interference screws, tissue fasteners, staples and other tissue and fracture fixation devices which are bioresorbable. Reference herein to a material being "bioresorbable" means that it breaks down over a finite period of time due to the chemical/biological action of the body. Preferably, complete resorption occurs within about 5 years, More preferably within about 3 years. This breakdown is at a rate allowing the repair device to maintain sufficient integrity while the soft tissue or bone heals: surgical repair devices formed of materials which are resorbed too quickly may fail when compressive, tensile or flexural loads are placed on them before the tissue or bone has fully healed. Advantages of using bioresorbable materials over non-bioresorbable materials, e.g. metals, are that they encourage tissue repair and further surgery is not required to remove them. In addition, there is the issue of stress-shielding: tissues like bone tend to grow well in regions where there is a prevalence of high stress. If the stress is reduced or removed, because, for example, an implant is bearing all the load, then the tissue may tend to recede around it resulting in loosening over the longer term. Implanted bioresorbable materials do not tend to give rise to adverse effects due to stress-shielding.

It is known to use certain bioresorbable polymeric materials, like polyglycolic acid (PGA) and polylactic acid (PLA), for

manufacturing surgical devices. These have the disadvantage, however, that they are brittle.

In addition, it is known to form blends of these materials and others, e.g. polycaprolactone (PCL), polytrimethylene carbonate (PTMC) and polydioxanone (PDO), to achieve desired physical attributes, like melting point and mechanical properties. It can prove difficult, however, to achieve the desired bioresorption rate of such materials in vivo.

Reference is also made to US 5 475 063, which teaches a blend of a bioresorbable random copolymer and another bioresorbable polymer. This is not only the stated aim of this document, but in all the examples manufacture of the copolymer is by non-sequential addition of the components, i.e. a random copolymer will result.

It is an object of the present invention to provide polymers, particularly for medical applications, with desirable mechanical and resorption properties.

According to a first aspect of the invention, a bioresobable polymeric composition is presented comprising a blend comprising a first bioresorbable polymer and a second, bioresorbable polymer, wherein the first bioresorbable polymer is a block copolymer.

Polymer blends are usually classified as either miscible or immiscible. Many combinations of polymers form immiscible blends, this being determined by a delicate balance of entropic and enthalpic forces of the blended polymers. The compatibility of two polymers in a mobile phase depends mainly on the forces acting

between the various groups in the chains of the same material as well as between the groups in the chains of the two different materials. In non-polar or weakly polar polymers the physical forces acting are principally dispersion forces. Therefore, when two non-polar polymers in a mobile isotropic liquid state are mixed together in a blend, phase separation into a dispersed and a continuous phase usually occurs. This phase separation is referred to herein as "macrophase separation".

The physical behaviour of block copolymers is related to solid state morphology. Block copolymers sometimes exhibit phase separation which typically gives rise to a continuous phase consisting of one block type in a continuous matrix consisting of a second block type. In many applications, the dispersed phase consists of hard domains which are crystalline or glassy and amorphous, the matrix being soft and rubber-like. This phase separation is referred to herein as "microphase separation". For more details regarding phase separation in block copolymers, reference is made to D.C. Allport and W.H. Janes, "Block Copolymers", Applied Science Publishers Ltd., London, 1973.

In a blend of a block copolymer and another polymer, it is possible to have microphase separation within the block copolymer itself and macrophase separation between the copolymer and the other polymer. Reference herein to microphase-separated copolymer implies that the dimensions of the domains are in the size range of less than or equal to 500nm. Reference herein to macrophase separation implies domain sizes (i.e. domains of dispersed and continuous phases) in the size range of greater than or equal to 1 micron, unless a compatibiliser has been added, in

which case the dimensions of the domains domain sizes are larger than 500nm.

A blend of this type gives a large number of variables which may be altered, to allow the rate of bioresorption and desired mechanical properties to be precisely tailored to desired levels: not only may the second bioresorbable polymer and the at least two types of block of the first bioresorbable polymer be varied, but either polymer may form the dispersed or the continuous phase, providing even more scope for variation of the properties of the material.

As stated, the first bioresorbable polymer may form the dispersed phase or the continuous phase. Preferably, the first bioresorbable polymer forms the dispersed phase and the second bioresorbable polymer forms the continuous phase.

Advantageously, there is also microphase separation within the first bioresorbable polymer. This allows the possibility of selecting a block of the copolymer which resorbs relatively quickly, generating porosity and allowing tissue ingrowth. It also allows the possibility of having a further block of the copolymer which modifies the blend properties (e.g. toughens it).

Advantageously, the second bioresorbable polymer and each of the types of block of the first bioresorbable polymer have different resorption rates. This allows porosity to be generated by resorption in certain parts of the blend, but, at the same time, structural integrity to be maintained while this is occurring.

Most preferably, at least one of the types of block of the first bioresorbable polymer is selected to have a higher rate of resorption

than both the other type(s) of block of said first bioresorbable polymer and the second bioresorbable polymer.

The first resorbable polymer is a copolymer, for example a diblock (i.e. AB), triblock (i.e. ABA) or multiblock (e.g. ABC or segmented) block copolymer.

The bioresorbable repeating units of the first bioresorbable polymer may be selected from saturated or unsaturated esters, including orthoesters, carbonates, anhydrides, amides, ethers, or saccharides.

Advantageously, the repeating units of the first bioresorbable polymer are derived from cyclic monomers capable of undergoing ring opening followed by polymerisation. Preferred cyclic monomers are cyclic esters and carbonates, like lactide (LA), glycolide (GA), caprolactone (CL), p-dioxanone (p-DO) and trimethylene carbonate (TMC). The ring opening reaction has the advantage that it may produce higher molecular weight polymers which may have superior mechanical and degradation properties. In addition, polyesters and polycarbonates have the advantage that they degrade in vivo to produce non-toxic by-products like carbon dioxide and water.

More preferably, the block copolymers comprise GA and/or TMC. Most preferably, the block copolymer is PGA-PTMC-PGA, which will also be referred to herein as Polyglyconate B and, in one form, as MAXON B™. The PGA blocks degrade relatively rapidly in vivo to give porosity and allow tissue ingrowth, while the PTMC blocks provide rubber-toughening which helps maintain the structural integrity of the blended material.

According to an advantageous embodiment of this aspect of the invention, one of the types of block of the first biodegradable polymer has a glass transition temperature, T_g, above ambient temperature (about 25°C) and one has a glass transition temperature, T_g, below ambient temperature. Preferably, the block copolymer comprises an essentially rubber central block with a T_g below ambient temperature and semi-crystalline end blocks with a T_g above ambient temperature.

The first biodegradable polymer may be a linear or non-linear block copolymer or comprise linear and non-linear portions. If it is non-linear, it may be formed as a star, comb, graft, brush, hyperbranched or "hairy" block copolymer or of mixtures thereof.

The weight average molecular weight (M_w) of the first biodegradable polymer of the present invention may be in the range 30,000 to 3,000,000. Preferably, it is in the range 50,000 to 1,000,000.

Advantageously, the first biodegradable polymer of the present invention has an inherent viscosity of between 0.5 and 4.0 dL/g.

The second biodegradable polymer of the present invention may be a homopolymer, block or random copolymer. It may be a linear or non-linear e.g. branched, star, brush, comb, graft, hyperbranched or 'hairy' polymer or mixtures thereof.

Preferably, the second biodegradable polymer is a resorbable aliphatic polyester or polycarbonate. Again, these materials have the advantage that the decomposition products are non-toxic. More preferably, it comprises repeating units incorporating one or more of the following monomers: GA,p-DO,LA,TMC and CL. Again, these

cyclic monomers polymerise by ring opening to give high molecular weight polymers with superior mechanical and degradation properties. In addition, the second polymer may comprise hydroxybutyrate (HB) monomers.

Advantageously, the second biodegradable polymer biodegrades at a lower rate than the first biodegradable polymer, i.e. the second polymer is more resistant to hydrolytic degradation and holds its strength for longer than the first biodegradable polymer. The choice of the second biodegradable polymer can therefore be determined empirically once the first polymer has been chosen.

A particularly preferred second biodegradable polymer is PLA.

A highly preferred blend according to the present invention is PGA-PTMC-PGA with PLA.

The second biodegradable polymer may make up from 1 to 99% by weight of total composition of the final product. Preferably, it makes up 20% to 90% and even more preferably, 40% to about 90% by weight of the total composition of the final product.

The bioresorbable composition according to the present invention may optionally comprise a compatibiliser, i.e. a component that is effective at the interface between the continuous and dispersed phases of the macrophase to reduce the dispersed phase domain sizes. Advantageously, the compatibiliser is a polymer, preferably an AB block copolymer. Preferred polymers comprise repeating units incorporating at least one of the following monomers: GA, DO, LA, TMC, CL. It is particularly preferred that the compatilibilser comprise at least one repeating unit present in the first polymer and at least one repeating unit present in the second polymer.

Advantageously, the compatibiliser comprises from about 1 to about 10% by weight of the total composition, preferably less than 5%wt of the total composition. It is also preferred that the compatibiliser have a weight average molecular weight (M_w) less than that of both the first and second polymers separately. This facilitates better interfacing of the compatibiliser between the dispersed and continuous phases. With this in mind, the compatibiliser preferably has an M_w of less than 100,000, more preferably less than 50,000.

The blend of the present invention may further comprise an inorganic filler such as calcium based salts to improve the osteoconductivity of the final product. Suitable calcium-based salts include calcium carbonate in various forms, especially aragonite, calcium phosphate, calcium sulphate, hydroxyapatite, BIOGALSS™ and the material 45S5™ produced by MO-SCI Corp. The filler of the present invention may be in particle form. Preferably, the average particle size is less than 1mm, more preferably, less than 200 microns. The blend of the present invention may comprise between about 10 to about 60% by volume of filler.

A second aspect of the invention relates to medical devices such as sutures, surgical fasteners, clips, sutures, staples, plates, screws e.g. interference screws, rods, pins and tapes, comprising the above-defined blends.

A third aspect of the invention relates to a surgical procedure comprising the step of incorporating a medical device, as defined above, into a tissue defect in a human or animal body.

A fourth aspect of the invention relates to methods of manufacture of the above-defined blends.

According to a first method, the first and second polymers are heated to form first and second polymer melts then said melts are blended. Optionally, said blend may be extruded, for example through a tapering die. The resulting blended workpiece may be subjected to one or more of the steps of granulation, drying and injection moulding to form a final product.

According to a second method, a solvent is selected in which both first and second polymers are soluble. The second polymer is added to said solvent and agitated until it is dissolved, at which point the first polymer, the block copolymer, is added to the solution and subjected to agitation. Suitably, agitation is carried out for up to one hour, preferably about 30 minutes. The solvent is then evaporated. Preferably, this is carried out in gradual stages involving one or both of natural evaporation and an evaporator, preferably a rotor evaporator. Finally, the blend is placed in a vacuum oven and heated to remove the residual solvent. Appropriate conditions for this are for a temperature of 80°C for about 2 hours.

Reference is made to the figures, which illustrate various aspects of the invention, as follows:

Fig.1 illustrates in graphical form the results of Table 1, below.

Fig.2 illustrates in graphical form the results of Example 2, below.

Fig.3 illustrates in graphical form the results of Table 3, below.

Fig.4 is a x1500 TEM photograph of the surface of a tensile fracture surface of a sample of polyglyconate B after a 10 week degradation, as described in the Degradation Protocol of Example 4, below.

Fig.5 is a x1500 TEM photograph of the surface of a tensile fracture surface of a sample of p-PLA after a 10 week degradation, as described in the Degradation Protocol of Example 4, below.

Fig.6 is a x1500 TEM photograph of the surface of a tensile fracture surface of a sample of a polyglyconate B / p-PLA blend in the ratio 40:60 after a 10 week degradation, as described in the Degradation Protocol of Example 4, below.

Fig.7 is a x8000 SEM image of a PLA/Polyglyconate B (MAXON B™) blend comprising 20%wt. PLA and 80%wt. Polyglyconate B.

Reference is made to the following examples which illustrate various aspects of the invention. It is stressed that the invention is not limited to these examples.

Example 1

Manufacturing Protocol

The compounding was carried out in a PRISM TSE-16-TC twin set extruder fitted with a 16mm diameter screw having an aspect ratio of 25:1 L/D with a barrel temperature of 220°C and a die temperature of 210°C. The feed was fed using discrete mechanical feeders and was mixed at a screw speed of 225 rpm. The extrudate was removed by a caterpillar belt and granulated using a prism microgranulator. The resulting polymer blend was dried and injection moulded to yield a suitable test bar.

Example 1(a)

A blend of PLA (65% by weight of total blend) and MAXON B™, i.e. PGA-PTMC-PGA, (35% by weight of total blend) was made according to the above manufacturing protocol.

Example 1(b)

A blend of PLA (35%) and PGA-PTMC-PGA (65%) was made according to the above manufacturing protocol.

Example 1(c)

A blend of PLA (80%) and PGA-PTMC-PGA (20%) was made according to the above manufacturing protocol.

Control samples of PGA-PTMC-PGA (100%) and PLA (100%) were also produced.

Example 1(d)

Blends of PLA/MAXON B™ were made according to the above manufacturing protocol, each blend comprising a proportion of compatibiliser (PLA-co-TMC) or (PLA-co-PGA), as detailed in Table 2, below.

Degradation Protocol

Degradation of the samples from Examples 1(a) - (d) and the controls was measured to analyse the ability of each sample to maintain its strength over a period of time. Measurement was according to the following degradation protocols: degradation of the samples at time points 0, 2 and 4 weeks from manufacture was established. Degradation was carried out as follows: samples were placed in a container of phosphate buffer solution (PBS, 100ml), and kept in an agitating incubator at 37°C. At the relevant time, the samples were removed from the PBS, dried and tested for maximum stress according to the testing protocol described below.

Mechanical Testing Protocol

Six injection moulded samples from each of examples 1(a) to (d) were tested in a Zwick 1435 tensile testing machine with a 5kN load cell and a test speed 50mm/min at room temperature and using an optical extensometer to measure displacement. The sample was placed in wedge action grips and tested for maximum stress.

Results

Results for Examples 1(a) to (c) and the controls are presented in Table 1 and represented in Fig.1. Results for Example 1(d) are presented in Table 2.

Table 1: Degradation study for PLA/Maxon B blends at time points 0, 2 and 4 weeks in PBS solution.

Material	Stress [MPa]		
	Time 0	2 weeks	4 weeks
Maxon B, 100%	60 ± 2	44 ± 4	2.5 ± 1
35:65 PLA:Maxon B	53 ± 3	43 ± 1	15 ± 1
65:35 PLA:Maxon B	64 ± 1	51 ± 1	31 ± 1
80:20 PLA:Maxon B	71 ± 1	59 ± 1	42 ± 1
100% PLA	78 ± 1	71 ± 2	56 ± 6

Table 2: Degradation study for PLA/Maxon B/ Compatibiliser blends at time points 0, 2 and 4 weeks in PBS solution.

	Stress [MPa]		
	Time 0	2 weeks	4 weeks
3.5% LA-co-TMC in 31.5:65 PLA:Maxon	54 ± 1	45 ± 1	14 ± 2
3.5% LA-co-GA in 31.5:65 PLA:Maxon	58 ± 1	47 ± 1	14 ± 1
2% LA-co-TMC in 18:80 PLA:Maxon	54 ± 1	40 ± 1	10 ± 1
2% LA-co-GA in 18:80 PLA:Maxon	54 ± 3	37 ± 2	8 ± 1

Example 2

Manufacturing Protocol - as for Example 1.

Example 2(a)

A blend of PLA / MAXON B™[80%wt/20%wt] was made according to the above manufacturing protocol.

Example 2(b)

A blend of PLA / MAXON B™[65%wt/35%wt] was made according to the above manufacturing protocol.

Degradation Protocol

Degradation of the samples from Examples 2(a) and 2(b) was measured to analyse the ability of each sample to maintain its strength over a period of time. Measurement was according to the following degradation protocols: degradation of the samples at time points 0, 2,4,8,12 and 24 weeks from manufacture was established. Degradation was carried out as follows: samples were placed in a container of phosphate buffer solution (PBS, 100ml), and kept in an agitating incubator at 37°C. At the relevant time, the samples were removed from the PBS, dried and tested for maximum stress according to the testing protocol described below.

Mechanical Testing Protocol - as for Example 1

Results

For ease of presentation, the results from Examples 2(a) and 2(b) as well as the controls are presented in the form of a graph only - see Fig.2.

Example 3

Manufacturing Protocol

The compounding was carried out in a PRISM TSE-16-TC twin set extruder fitted with a 16mm diameter screw having an aspect

ratio of 25:1 L/D. The hopper temperature and temperature of the zones was 215°C and the die temperature was 210°C. Die pressure was 30-40 Bar. The feed was fed using discrete mechanical feeders and was mixed at a screw speed of 225 rpm. The extrudate was removed by a caterpillar belt and granulated using a prism microgranulator. The resulting polymer blend was dried and injection moulded to yield a suitable test bar.

Example 3(a)

A blend of polycaprolactone / MAXON B™ (65%/35%) was made according to the above manufacturing protocol.

Example 3(b)

A blend of PLA and P(ga/la-tmc-ga/la) (65%/35%) was made according to the above manufacturing protocol.

Control samples of polycaprolactone (100%) and p-PLA (100%) were also produced.

Degradation Protocol

Degradation of the samples from Examples 3(a), 3(b) and the controls was measured to analyse the ability of the sample to maintain its strength over a period of time. Measurement was according to the following degradation protocol: degradation of samples at time points 0, 4 weeks and 7 weeks from manufacture was carried out as follows. Samples were placed in a container of phosphate buffer solution (PBS, 100ml), and kept in an agitating incubator at 37°C. At the relevant time, the samples were removed from the PBS, dried and tested for maximum stress according to the testing protocol described below.

Mechanical Testing Protocol

Four to six injection moulded samples from each of examples 1 to 4 were tested in a Zwick 1435 tensile testing machine with a 5kN load cell and a test speed 50mm/min at room temperature and using

an optical extensometer to measure displacement. The sample was placed in wedge action grips and tested for maximum stress.

Results

The results from Examples 3(a) and 3(b) as well as the controls are presented in Table 3 and represented in Fig.3.

Table 3: Degradation study for PCL/Maxon B and PLA/P(GA/LA-TMC-GA/LA) blends at time points 0, 2 and 7 weeks in PBS solution.

Material	Maximum Stress [MPa]		
	Time 0	4 weeks	7 weeks
Polycaprolactone (PCL)	16±2	18±1	18±1
PCL/MAXON B	17.1±0.5	13.4±1	1±2
PLA	83.6±0.3	78±2	77.8±1.2
PLA/P(GA/LA-TMC-GA/LA)	54±5	27.9±1.1	28.9±0.7

Example 4

Manufacturing Protocol

Samples of (a) Polyglyconate B (i.e. PGA-PTMC-PGA), (b) p-PLA and (c) a Polyglyconate B / p-PLA blend in the weight ratio 40:60 were produced according to the protocol described in Example 1.

Degradation Protocol

The above materials were subjected to degradation for 10 weeks at pH 7 and 37°C followed by further degradation for 4 weeks at pH 3 and 50°C.

Results

Preliminary transmission electron microscopy (TEM) analysis was carried out on degraded blend tensile fracture samples (a), (b)

and (c). With reference to Figures 4-6, it was found that PLA (see Fig.4) and polyglyconate B (see Fig.5) were still composed of a single phase, while the blend had developed a honeycomb structure (see Fig.6).

From the maximum stress data gained in relation to the single second polymers, PLA and PCL - see Figs. 1 and 3 - it is evident that bioresorption, as measured in terms of maximum stress, is occurring slowly. Fig.1 also illustrates that particularly PLA on its own has a high maximum stress, so is capable of providing the high strength required in certain implants. Polycaprolactone has a lower strength, illustrating that it is possible to tailor such properties to the requirements at hand.

Considering the blends, it is apparent that the rate of bioresorption of the second polymer can be significantly modified by addition of the first polymer, the block copolymer. With reference to Figure 1, it is evident that the rate of degradation can be increased by increasing the proportion of MAXON B™ in the blend. With reference to Fig.3, it is evident that the same effect can also be achieved by adding MAXON B™ to polycaprolactone. Comparing the results for polycaprolactone/MAXON B™(65/35) with those of PLA/MAXON B™(65/35), it can be seen that a lower initial strength for polycaprolactone/MAXON B™(65/35) is offset by a high rate of resorption, again showing that it is possible to tailor materials to achieve a balance of strength and rate of bioresorption.

The same sort of effects achieved by adding MAXON B™ to the second polymer are also achieved by blending in other block copolymers, as can be seen from Fig.3.

With reference to Table 2 and comparing the first two materials with the result from Table 1 relating to PLA/MAXON B™ (35/65), there is some indication of a slightly faster degradation rate, although this particular comparison is not very conclusive. In fact, other results have indicated that use of the compatibiliser can increase the degradation rate of the blend. While not wishing to be bound by any theory, this is believed to be due to the increased surface area of contact between the dispersed and continuous phases (in the macrophase separated dispersion), due to the smaller domain sizes of the dispersed phase, resulting from use of the compatibiliser.

With reference to Fig.2, degradation of the blend over the longer term is illustrated. The plateau-like region derives from the fact that the MAXON™ has mostly been degraded at this point leaving a porous honeycomb of PLA which itself degrades slowly over the ensuing weeks and months.

This honeycomb structure is illustrated in Fig.6. The porosity of the blend is due to the higher degradation rate of the PGA blocks in the polyglyconate B. The pore size was found to be dependent upon the blend ratio. For a Polyglyconate B/PLA blend in the ratio 40:60 pores in the 5-10 micron size-range were generated.

Although, as illustrated in Figs. 1,3 and 4, PLA on its own has a relatively slow rate of hydrolytic degradation, this material is found to degrade more rapidly when blended with a copolymer according to the invention, i.e. in situation like that illustrated in Figs.1 and 2, because of the increased surface area for degradation resulting from the honeycomb structure (Fig.6) remaining after degradation of the copolymer.

Lastly, reference is made to Fig.7. This SEM image illustrates islands of dispersed phase (1), PLA in this case, in a continuous phase of Polyglyconate B (i.e. PGA-PTMC-PGA or MAXON B™). It can clearly be seen that the continuous phase is, in fact, not a single phase but is also a dispersion due to the microphase separation. In this instance, light areas of semicrystalline PGA (2) are interspersed with dark areas of rubber-like PTMC (3). Although blends, as illustrated in this figure do fall under the scope of the invention, the preferred blends according to the present application are those in which the block copolymer forms the dispersed phase.

CLAIMS

1. Bioresobable polymeric composition comprising a blend comprising a first bioresorbable polymer and a second bioresorbable polymer, wherein the first bioresorbable polymer is a block copolymer.

2. Bioresorbable composition according to claim 1, wherein the blocks of the first bioresorbable polymer are saturated or unsaturated esters, orthoesters, carbonates anhydrides, ethers, amides or saccharides.

3. Bioresorbable composition according to claim 1 or 2, wherein the blocks of the first bioresorbable polymer are polyesters or polycarbonates.

4. Bioresorbable composition according to any one of the preceding claims, wherein the blocks of the first bioresorbable polymer are derived from cyclic monomers selected from the group comprising glycolide, dioxanone, lactide, trimethylene carbonate and caprolactone.

5. Bioresorbable composition according to any one of the preceding claims, wherein the copolymer blocks comprise polyglycolic acid or polytrimethylene carbonate.

6. Bioresorbable composition according to any one of the preceding claims, wherein the first bioresorbable polymer is PGA-PTMC-PGA.

7. Bioresorbable composition according to any one of the preceding claims, wherein the second bioresorbable polymer comprises a homopolymer, a block copolymer or a random copolymer.

8. Bioresorbable composition according to any one of the preceding claims, wherein the second bioresorbable polymer comprises a bioresorbable aliphatic polyester or polycarbonate.

9. Bioresorbable composition according to any one of the preceding claims, wherein the second bioresorbable polymer is derived from cyclic monomers selected from the group comprising glycolide, dioxanone, lactide, trimethylene carbonate, caprolactone.

10. Bioresorbable composition according to any one of the preceding claims, wherein the second bioresorbable polymer is polylactic acid.

11. Bioresorbable polymeric composition according to any one of the previous claims, wherein there is microphase separation within the first bioresorbable polymer and macrophase separation between the first and second bioresorbable polymers.

12. Bioresorbable composition according to any one of the previous claims, wherein the first bioresorbable polymer forms the dispersed phase and the second bioresorbable polymer forms the continuous phase.

13. Bioresorbable composition according to any one of the previous claims, wherein the second bioresorbable polymer and

each of the types of block of the first bioresorbable polymer all have different resorption rates.

14. Bioresorbable composition according to any one of the preceding claims, wherein one of the types of block of the first bioresorbable polymer is selected to have a higher rate of resorption than both the other type(s) of block of said first bioresorbable polymer and the second bioresorbable polymer.

15. Medical device comprising a bioresorbable composition according to any one of claims 1-14.

16. Surgical procedure comprising the step of incorporating the medical device of claim 15 into a tissue defect in a human or animal body.

17. Method of manufacture of the bioresorbable composition of claims 1-13, comprising the steps of heating the first and second polymers to form first and second polymer melts and blending said melts.

Fig.1

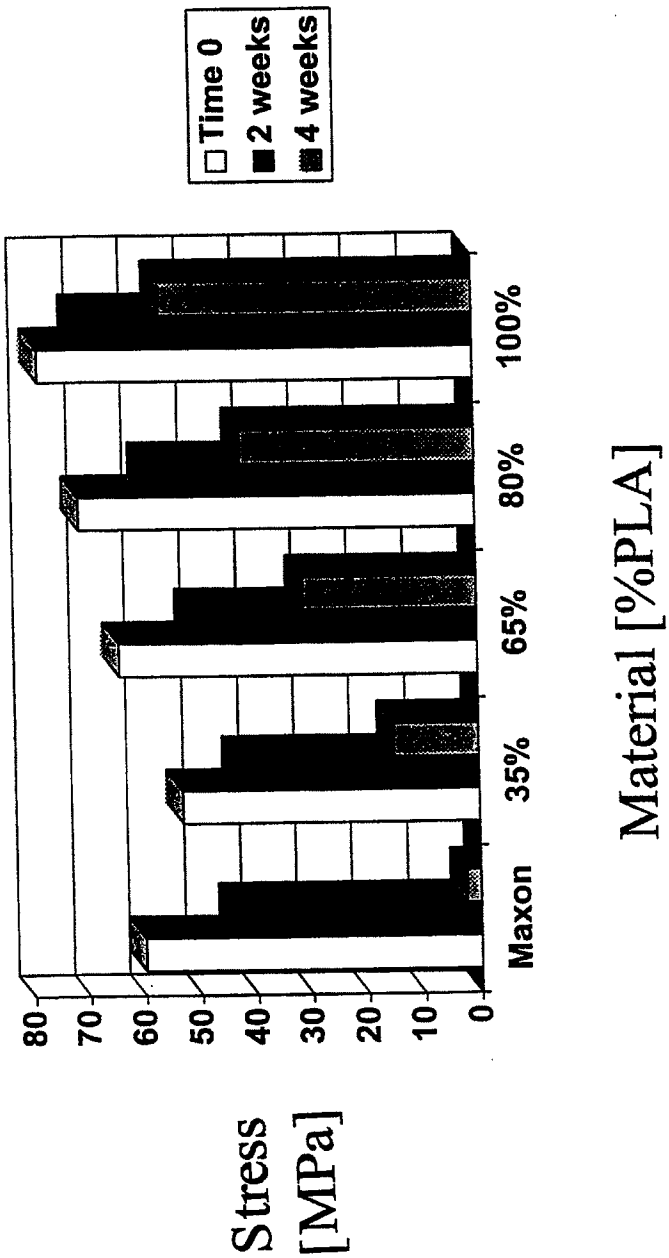

Time 0
2 weeks
4 weeks
80
70
60
50
40
30
20
10
0
Stress [MPa]
Maxon
35%
65%
80%
100%
Material [%PLA]

Fig.2

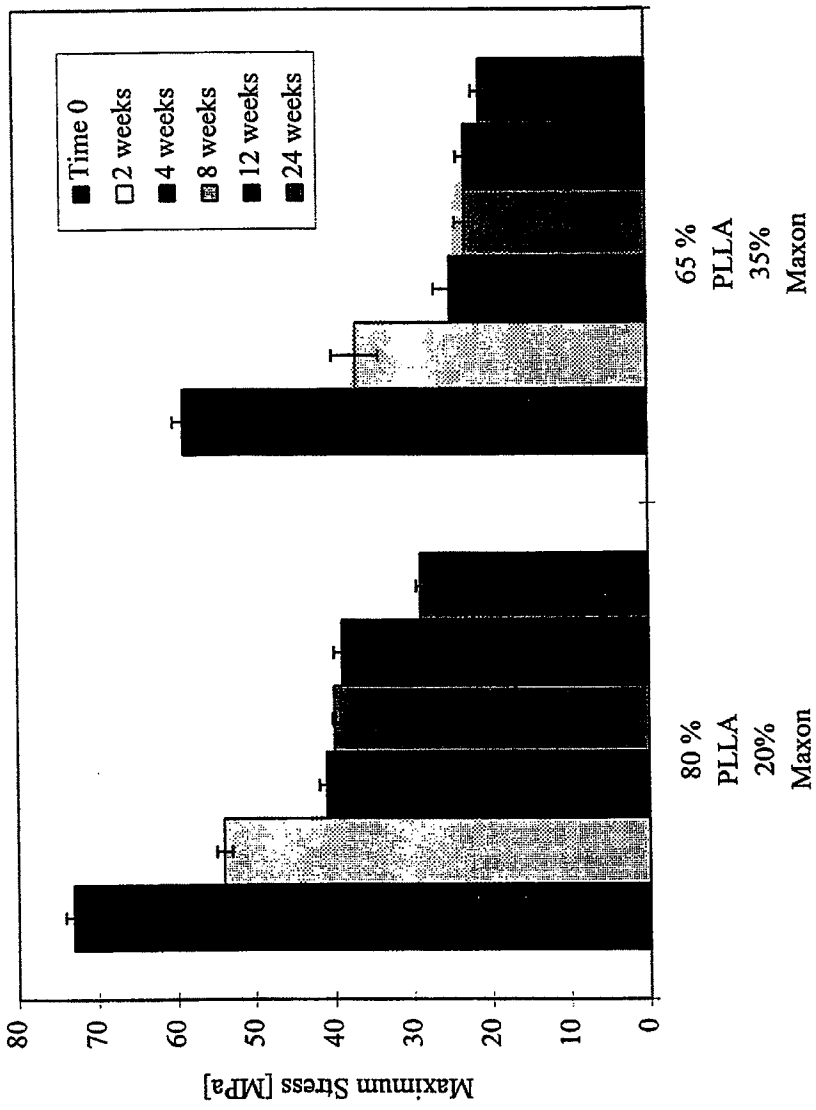

Time 0
2 weeks
4 weeks
8 weeks
12 weeks
24 weeks
Maximum Stress [MPa]
0
10
20
30
40
50
60
70
80
80 % PLLA 20% Maxon
65 % PLLA 35% Maxon

Fig.3

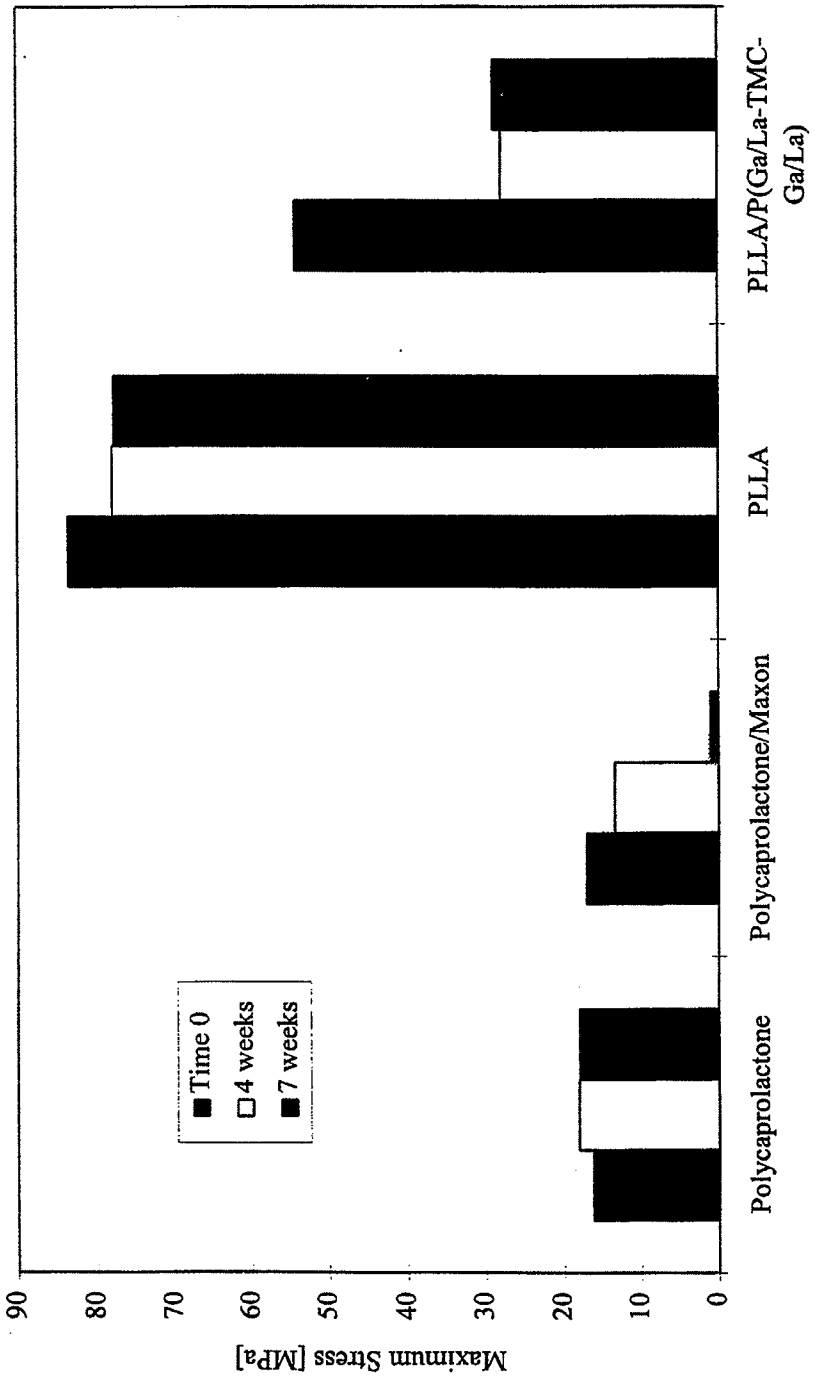
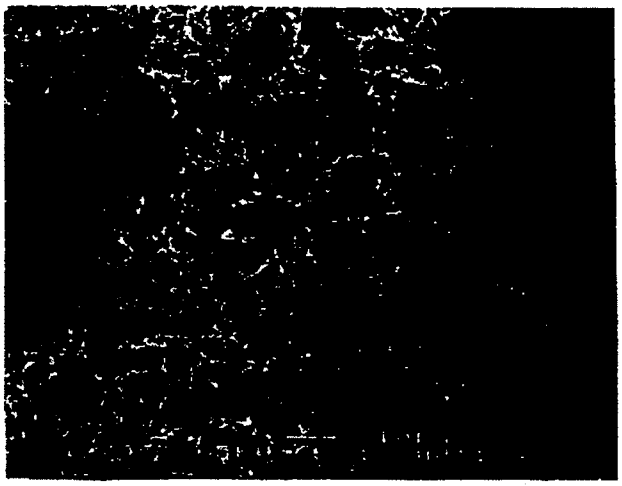

Maximum Stress [MPa]
0
10
20
30
40
50
60
70
80
90
Time 0
4 weeks
7 weeks
Polycaprolactone
Polycaprolactone/Maxon
PLLA
PLLA/P(Ga/La-TMC-Ga/La)

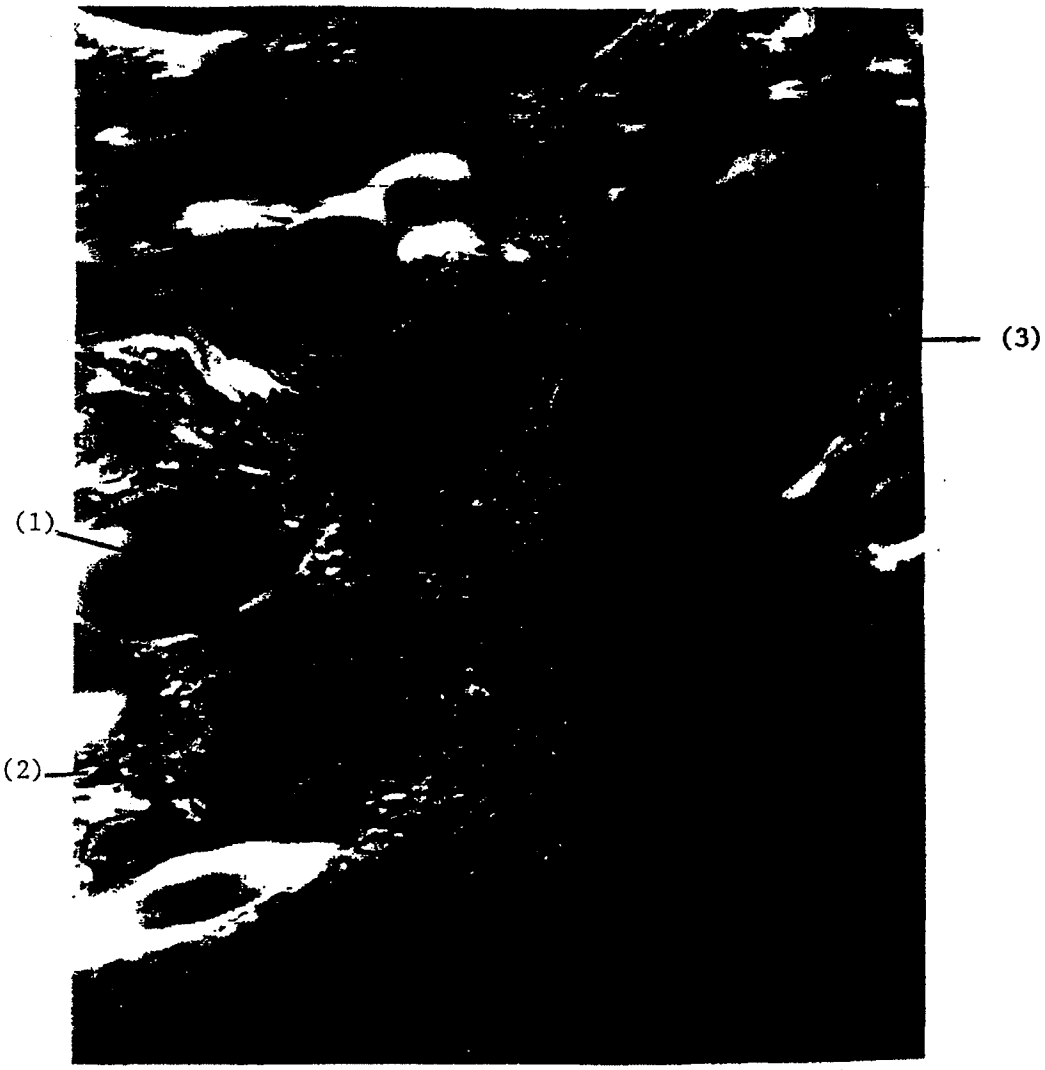
Fig.4

Fig.5

Fig.6



5/5
Fig. 7



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02154

A. CLASSIFICATION OF SUBJECT MATTER
IPC-7 A61L17/00 A61L31/00 C08L69/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 713 708 A (UNITED STATES SURGICAL CORP) 29 May 1996 (1996-05-29) abstract column 3, line 36-45 column 4, line 58 -column 5, line 27,55-59 column 6, line 1-23 claim 6; example 1 ---	1-5, 7-12,15, 17
X	US 5 475 063 A (KAPLAN DONALD S ET AL) 12 December 1995 (1995-12-12) abstract column 2, line 32-67 column 3, line 1-23 column 5, line 14-19; examples --- -/--	1-5, 7-10,15, 17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 1999	21/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Böhm, I

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte· ·tional Application No
PC·/GB 99/02154

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication.where appropnate. of the relevant passages	Relevant to claim No.
X	US 5 531 998 A (MARES FRANK ET AL) 2 July 1996 (1996-07-02) abstract column 1, line 11-14 column 3, line 31-62 column 13, line 49 -column 14, line 9	1-5, 7-10,15
X	US 4 429 080 A (CASEY DONALD J ET AL) 31 January 1984 (1984-01-31) abstract column 1, line 39-43 column 2, line 16-65 column 3, line 41-64	1-7,9,15
A	US 4 243 775 A (ROSENSAFT MICHAEL N ET AL) 6 January 1981 (1981-01-06) abstract column 2, line 11-23 column 4, line 10-26	1-5,9, 10,15
A	WO 89 05664 A (ALLIED SIGNAL INC) 29 June 1989 (1989-06-29) abstract page 1, line 6-13 page 4, line 4-7 page 6, line 9-13 page 8, line 17-19 page 25, line 4,5	1-5, 7-10,13, 15

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB 99/02154

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inte ·ational Application No
PC·/GB 99/02154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0713708 A	29-05-1996	US 5607686 A	04-03-1997
		CA 2161196 A	23-05-1996
US 5475063 A	12-12-1995	US 5320624 A	14-06-1994
		CA 2079274 A	31-03-1994
		CA 2060635 A	13-08-1992
		DE 69202584 D	29-06-1995
		DE 69202584 T	07-12-1995
		EP 0499204 A	19-08-1992
		US 5674286 A	07-10-1997
US 5531998 A	02-07-1996	CA 1338650 A	15-10-1996
		US 5120802 A	09-06-1992
		DE 3853591 D	18-05-1995
		DE 3853591 T	14-09-1995
		EP 0390860 A	10-10-1990
		WO 8905664 A	29-06-1989
		US 4891263 A	02-01-1992
		US 4916193 A	10-04-1990
		US 4916207 A	10-04-1990
		US 5412068 A	02-05-1995
		US 5486593 A	23-01-1996
		US 5145945 A	08-09-1992
		US 5066772 A	19-11-1991
		US 5185408 A	09-02-1993
		US 5152781 A	06-10-1992
		US 5256764 A	26-10-1993
		US 5274074 A	28-12-1996
		JP 2868817 B	10-03-1999
US 4429080 A	31-01-1984	AU 565928 B	01-10-1987
		AU 1640683 A	05-01-1984
		BR 8303522 A	07-02-1984
		CA 1204894 A	20-05-1986
		DK 302083 A,B,	02-01-1984
		EP 0098394 A	18-01-1984
		ES 523618 A	01-11-1984
		FI 832405 A,B,	02-01-1984
		JP 59014855 A	25-01-1984
		NZ 204713 A	11-07-1986
		PH 18703 A	05-09-1985
		ZA 8304803 A	28-03-1984
US 4243775 A	06-01-1981	AU 526436 B	13-01-1983
		AU 4227378 A	22-05-1980
		DD 140982 A	09-04-1980
		DE 2850824 A	22-05-1980
		FR 2440959 A	06-06-1980
		GB 2033411 A	21-05-1980
		IT 1157718 B	18-02-1987
		JP 1497639 C	29-05-1989
		JP 62215625 A	22-09-1987
		JP 63047731 B	26-09-1988
		JP 55066923 A	20-05-1980
		NL 7811499 A	16-05-1980
		NZ 190164 A	16-03-1981
		US 4300565 A	17-11-1981

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8905664 A	29-06-1989	CA 1338650 A	15-10-1996
		US 4891263 A	02-01-1990
		US 5120802 A	09-06-1992
		US 4916193 A	10-04-1990
		US 4920203 A	24-04-1990
		DE 3853591 D	18-05-1995
		DE 3853591 T	14-09-1995
		EP 0390860 A	10-10-1992
		US 5531998 A	02-07-1990
		US 4916207 A	10-04-1990
		US 5412068 A	02-05-1995
		US 5486593 A	23-01-1996
		US 5145945 A	08-09-1992
		US 5066772 A	19-11-1991
		US 5185408 A	09-02-1993
		US 5152781 A	06-10-1992
		US 5256764 A	26-10-1993
		US 5274074 A	28-12-1996
		JP 2868817 B	10-03-1990